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AMINOPHOSPHONIC ACID CONTAINING INHIBITORS OF HUMAN COLLAGENASE: MODIFICATION OF THE P_1 RESIDUE

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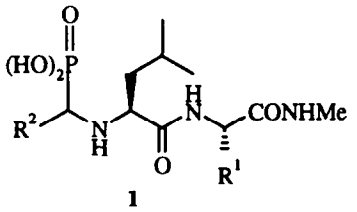
Abstract

A series of peptidomimetic aminophosphonic acid derivatives was synthesized and evaluated *in vitro* for inhibition of human fibroblast collagenase activity. Incorporation of a bromonaphthalimidoethyl moiety at the P_1 position led to potent inhibitors, such as **14a** (IC_{50} 0.02 μM).

Introduction

Collagenase (MMP-1) is a member of the family of zinc-containing matrix metalloproteinases (MMPs) and is thought to play a major role in the destruction of connective tissue components of articular cartilage.[1] Synthetic inhibitors of collagenase and stromelysin/proteoglycanase (MMP-3)[2] are important targets in drug discovery[3] in diseases such as rheumatoid arthritis and osteoarthritis.



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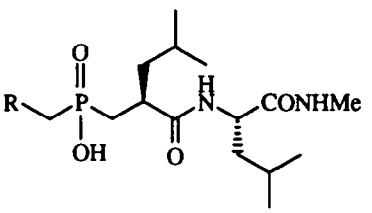
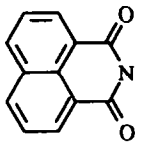


2a, R = MeCONH

2b, R =



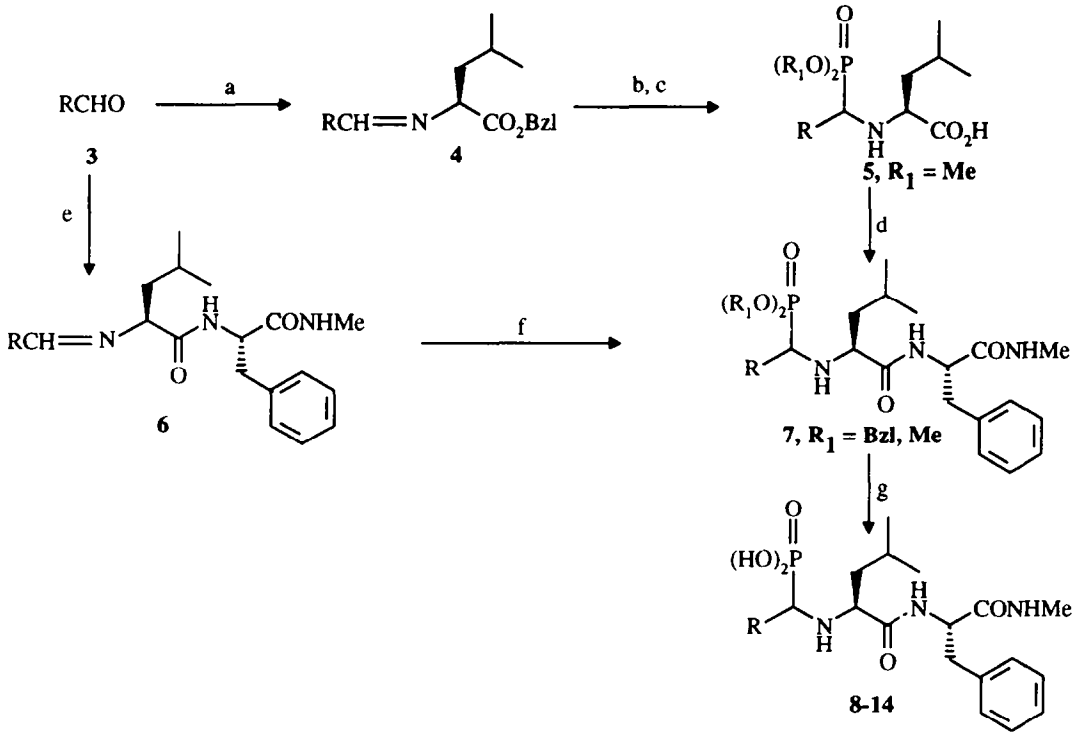
Previous work in our laboratories led to the development of a series of *N*-phosphonoalkyl dipeptides **1** that are potent inhibitors *in vitro* of human collagenase.[4] A number of other small molecule inhibitors have been described.[5,6] In particular, phosphinic acids such as **2a**[7] are relatively weak collagenase inhibitors *in vitro* (IC_{50} 37μM), but potency is enhanced (~ 20-fold) in compounds such as **2b** when a naphthalimido group is incorporated at the P_1 position.[7,8] In this paper, we describe a series of aminophosphonic acid analogs **10-14**, containing phthalimido or naphthalimido substituents at the P_1 position, and their ability to inhibit the

degradation of radiolabeled collagen by purified human lung fibroblast collagenase.[9]

Chemistry

Residues known[4] to impart potent collagenase inhibitory activity were incorporated at the P_1' and P_2' positions, and modification of the P_1 substituent was investigated. The aminophosphonic acids **8-14** and the aminophosphinic acid **15** were prepared by previously described methods,[4] as outlined in scheme 1. Phosphite addition to the imines **4** and **6** was achieved via a silyl phosphite intermediate.[10] Where possible, the two diastereoisomers were separated by chromatography on silica gel and the stereochemistry of single diastereoisomers was assigned by a comparison of proton chemical shifts with compounds of known stereochemistry.[4]

Scheme 1

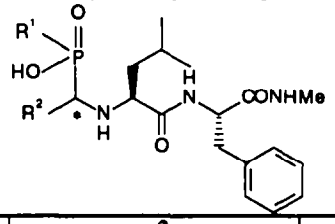


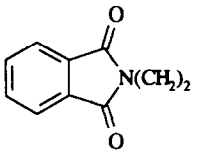
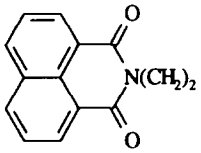
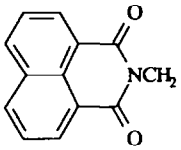
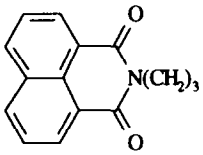
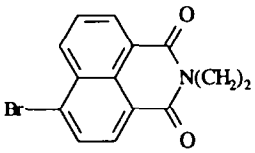
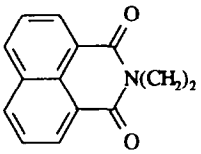
Reagents: (a) LeuOBzl, CH_2Cl_2, $MgSO_4$; (b) $P(OMe)_2OTMS$, CH_2Cl_2, 0°C; (c) H_2, 10%Pd/C, MeOH; (d) PheNHMe, EDC, HOBt, CH_2Cl_2; (e) LeuPheNHMe, CH_2Cl_2, $MgSO_4$; (f) $P(OBzl)_2OTMS$, CH_2Cl_2, 0°C; (g) H_2, 10%Pd/C, EtOH; or TMSBr, CH_2Cl_2.

Results and Discussion

We previously determined[4] that for compounds such as **8a** and **8b**, containing P_1 alkyl substituents, the stereochemistry of the centre α to phosphorus did not markedly influence potency. However, the introduction of a phenethyl substituent in compounds such as **9a** and **9b** produced a 5-fold difference in potency between

Table. Collagenase Inhibitory Potency of Phosphonic and Phosphinic Acids



Compound	R^1	R^2	*	IC_{50}[9], μM
8a	HO	Et	R	0.23
8b			S	0.24
9a	HO	$Ph(CH_2)_2$	R	0.40
9b			S	1.82
10a	HO		R	0.19
10b			R,S	0.36
11a	HO		R	0.03
11b			S	0.15
12	HO		R,S	2.12
13	HO		R,S	0.73
14a	HO		R	0.02
14b			S	1.63
15	H		R,S	>100

P_1 diastereoisomers, with the *RSS* stereochemistry preferred.

In order to investigate the effect of other bulky substituents at the P_1 position, a series of compounds was prepared and their *in vitro* activities are shown in the Table. Compounds **10a** and **10b**, containing a phthalimidoethyl group, exhibited similar potency to the phenethyl compound **9a**. However, the introduction of a naphthalimidoethyl group in compounds **11a** and **11b** increased potency approximately 10-fold over **9a** and **9b** respectively, and there was a 5-fold difference in potency between the two diastereoisomers. Interestingly, as in our previous series of compounds,[4] the analogous aminophosphinic acid **15**, containing a naphthalimidoethyl at the P_1 position, was essentially devoid of activity. The effect of varying the chain length was investigated and potency was found to be reduced in both compounds **12** and **13**. The bromonaphthalimidoethyl analog **14a** (*RSS* isomer) was the most potent compound in the series and was 80-fold more potent than **14b** (*SSS* isomer). As with **8a** and its carboxyalkyl analogue,[4] **14a** appears to be 10-fold more potent than the corresponding carboxyalkyl compound.[6] X-ray crystallographic studies of human recombinant collagenase complexed to an inhibitor, containing a hydroxamic acid zinc ligand, have shown a hydrogen-bonding interaction between an asparagine residue at the active site and the imide carbonyl of a phthalimido group at the P_1 position.[11] A similar favourable interaction may be responsible for the potency of compounds **11a** and **14a** (*RSS* isomers). By contrast, it is interesting that the introduction of a bromo substituent in the naphthalimido ring in the *SSS* series (cf. **14b** and **11b**) results in a 10-fold decrease in activity.

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